C-Reactive Protein as a Clinical Marker of Risk

To the Editor:

We read with great interest the article by Lagrand et al1 in which the authors both review the role of C-reactive protein (CRP) as a marker of cardiovascular risk and propose a pathogenetic role for CRP. Although the evidence reviewed by Lagrand et al1 convincingly suggests an association between CRP and cardiovascular risk, we are concerned that the authors appear to assume that CRP is an established, independent risk factor and that its measurement has defined clinical applications.

Although it has been shown in large epidemiological studies that high concentrations of CRP are associated with increased cardiovascular risk in both patients with coronary artery disease and apparently healthy individuals, extrapolation of findings in large epidemiological studies to the clinical setting may not be straightforward. One of the difficulties for the application of “epidemiological” results to the individual patient relates to the lack of well-established CRP levels that can be considered to represent accurate cutoff points to identify the individual patient at risk. Different studies have used different analytical assays, and therefore CRP levels vary significantly among these studies. For example, mean CRP levels in apparently healthy men who developed cardiovascular events were reported in one study to be 1.40 mg/L,2 whereas another study3 in patients with unstable angina considered a value of 15.5 mg/L to represent the cutoff level between low and high risk. Another difficulty is that despite suggestions of stable CRP levels over time within individuals, there are reports indicating that the intragroup variability of CRP may be high (between 42% and 63%).4 This finding of high intragroup variability in CRP levels is important in view of the fact that in the large epidemiological studies, CRP concentrations differed only slightly, albeit significantly, between individuals with increased risk of cardiovascular events and those with low risk. The issue of intragroup CRP variability requires further investigation in large studies. If the large variability is confirmed, strategies for the use of CRP as a prognostic marker in the individual patient should be planned carefully.

Despite the convincing evidence of a relationship between CRP concentrations and cardiovascular risk in large studies, CRP, as well as other acute-phase reactants, is a nonspecific marker of inflammation. A recent meta-analysis5 has shown that fibrinogen, CRP, albumin (inverse relation), and leukocyte count were all strongly related to cardiovascular risk. These observations suggest that these markers may be closely interrelated and represent only a nonspecific indication of inflammation and/or other mechanisms underlying the atherogenic process.

Lagrand et al1 propose a most interesting pathogenetic hypothesis involving CRP in atherogenesis and rapid coronary artery disease progression. Their suggestion that CRP may have a causal role is intriguing and clearly deserves further investigation in well-designed studies. Undoubtedly, a better understanding of the pathogenic role of CRP in ischemic heart disease may help to speed up the process leading to the successful use of CRP as a clinical marker of risk. At present, however, the use of CRP as a prognostic marker in the individual patient (or the apparently healthy subject) has limitations.

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